## MRI in Multiple Sclerosis: From diagnosis to prognosis

Korteweg, T.

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# Summary and General discussion

## Summary

The main goal of this thesis was to investigate the diagnostic process and the mechanisms of disease progression in the various subtypes of multiple sclerosis (MS). To establish this, MRI derived metrics for brain damage were studied on different levels: from macroscopic lesion formation in the earliest stage of the disease (part I), through nonconventional MRI (atrophy) measurements in early and relapsing-remitting multiple sclerosis (RRMS) to potential recovery mechanisms of the brain as measured by functional MRI (fMRI) (part II). Most studies were carried out as part of the European Community network for Magnetic Resonance research in MS (MAGNIMS).

## Summary of findings

*Diagnosis*

In the initial stage of the disease, MRI findings can give additional information about the risk of conversion from a clinically isolated syndrome (CIS) to clinically definite multiple slecrosis (CDMS). The presence of lesions that suggest a demyelinating disease is associated with high risk of developing CDMS (about 55–80% at 10–20 years); whereas the absence of lesions is associated with a low risk (roughly 20%).[1, 2] Lesions giving the greatest risk of early conversion were defined in the (modified) Barkhof cumulative chance model and incorporated in the International Panel (IP) diagnostic scheme for the diagnosis of MS as evidence for dissemination in space (DIS).[3-5] However, the Barkhof MRI model was developed from a cohort with a relatively limited number of patients from a small number of different sites. To further study the performance of the modified Barkhof criteria in a general setting we performed a retrospective multicenter follow-up study in patients with a CIS. The only requirements for inclusion were the availability of an MRI within three months from clinical onset and clinical follow-up data to assess the development of a second clinical event, ie CDMS.

In contrast to previous studies we made use of survival analysis, which allowed variable follow time between cases by censoring lost cases, as well as confounder adjustment. The results, presented in **chapter 1**, showed that patients fulfilling the criteria for DIS had a higher risk of conversion compared to patients with a normal scan or a minimally abnormal scan, the latter comprising the presence of at least one lesion in the CNS without fulfilment of any of the individual Barkhof criteria. These findings confirmed the results from previous studies in which the criteria were developed. On the contrary, although the specificity was maintained, the sensitivity was lower than previously reported. The added value of the current study is the confirmation of the specificity of the modified Barkhof model in a large number of cases, derived from normal clinical setting from multiple (European) centres. This is important as it suggests a low false positive rate for CDMS, avoiding unnecessary (early) treatment.

In addition to the diagnostic accuracy, the practical usability of diagnostic criteria in general is an important factor for acceptance and application in daily clinical use. Proper application of the MRI part of the IP diagnostic scheme requires correct lesion identification, evaluation of lesion location and assessment of new lesion formation over time. Finally, these findings need to be combined to reach a decision on the absence or presence of DIS and DIT. An interpretational difference in each of these steps could have an effect on the diagnostic accuracy. In **chapter 2** we studied the interpretational variation in the diagnosis of MRI based DIS, resulting from the somewhat ambiguous guidelines regarding the use of spinal cord MRI in the IP diagnostic scheme. The aim of this study was to determine whether application of the MRI part of the IP diagnostic scheme altogether by different users would lead to a variation in diagnosis and which components of the criteria would be most vulnerable for this variability. Two groups of experienced radiologists applied the criteria to a MRI dataset of CIS patients. The two groups of raters varied in their experience with the application of the IP diagnostic scheme, because one group was derived from hospitals in a general diagnostic setting (IP-naïve observers), whereas the second group was employed in an academic MS referral centre, being regularly involved in the MRI workup in cases of CIS. Outcome of this study led to the recognition that there is an interobserver difference between radiologists familiar with the IP diagnostic scheme and radiologists that are less familiar with the agreement. Less experienced radiologists do not reach the same level of agreement assessing DIS and DIT compared to radiologists who are more familiar with the scheme. This suggests that current criteria are complicated and therefore there is a need to simplify the IP diagnostic scheme. On the other hand, given the poor interobserver agreement among IP-naïve observers, radiologists evaluating the scans might benefit from training to reduce the variability of their findings.

In **chapter 3** the specificity of the MRI part of the IP diagnostic scheme was tested in a retrospective cohort of patients suspected by their own neurologist to have MS but who ultimately, after second opinion, received another diagnosis. As the modified Barkhof (MRI) criteria were developed in a cohort of CIS patients from which alternative diagnoses had been removed, they were thought to be less specific for MS. Follow-up studies have shown that up to 80% of CIS patients will experience a second relapse in the long term[6, 7] and the diagnostic criteria have been perceived as a parameter for disease prognosis rather than as an instrument to diagnose difficult cases.[8, 9] Alternatively proposed criteria, requiring the presence of three white matter lesions were assumed to provide higher sensitivity with equal specificity.[10] Our study applied the IP diagnostic scheme in diagnostically difficult cases, and revealed higher specificity compared to the newly proposed criteria, important when conformation of the disease is needed in routine clinical setting.

In conclusion, our studies confirmed the specificity of the modified Barkhof criteria as included in the IP diagnostic scheme, but revealed a somewhat lower sensitivity than expected from previous studies. Another drawback of the criteria is their relative complexity, requiring substantial experience of the user with the application of the criteria before they can be reliably used in a clinical setting. To overcome this problem we attempted to improve the diagnostic criteria by searching for other

characteristics in T2 lesion distribution in case of CIS, predicting conversion to CDMS **(chapter 4)**. The aim was to determine a set of criteria that would be easier to apply and that would be more sensitive while maintaining current specificity. We made use of advanced statistical modeling in the available MAGNIMS dataset as collected for the study presented in **chapter 1**. This resulted in decision models primarily based on deep with matter and the presence of periventricular T2 lesions. Although the new schemes were indeed less difficult to use, they were not able to increase overall accuracy. Including contrast enhancement status into analysis could have improved our findings, being a strong indicator for development of CDMS. However in our retrospective cohort this information was (largely) unavailable. We argued that baseline topological and morphological T2 lesions findings alone might contain to little information to improve diagnostic accuracy and that inclusion of findings from spinal cord MRI and follow-up scans might be helpful. Perhaps more lenient and simple criteria for DIS can be allowed when DIT is fulfilled, as can be derived from combination with follow-up scans. This has been further studied within the MAGNIMS network collaboration and is detailed in the general discussion.

*Prognosis*

In addition to being able to establish a diagnosis it is desirable to be able to predict disease progression since current treatment options can reduce disease activity and disease progression. Unfortunately, while the diagnostic criteria for MS have evolved into a readily applicable scheme giving guidance for clinicians, the prediction of future disease course and disability in MS remains challenging. In some cases, patients will progress into severe disability or even death within years after diagnosis, while other patients show minimal disability during longer follow-up after their first clinical event. This uncertainty is difficult to manage, for both patients and clinicians.

Conventional MRI has been used to refine the accuracy of prognosis in MS. Putative predictors that have been studied include numbers and volumes of lesions observed on T2 and T1 weighted images, as well as gadolinium contrast enhancement status. However, these measures only show weak correlations to the clinical status as expressed by the Expanded Disability Status Scale (EDSS) and are incapable of predicting clinical progression.[11-13] Attention has been drawn to other MRI measures and whole brain atrophy measurements have a stronger association with physical disability and better predict future disability than do T1-hypointense and T2-hyperintense lesion volumes.[14] Brain atrophy is regarded to best reflect neurodegeneration and represent the endpoint of irreversible tissue loss. However, the exact mechanisms leading to atrophy are largely unknown, and the volume loss is incompletely explained by MRI measures of inflammation as expressed by lesion volumes. Additionally, atrophy seems partially related with changes in the normal appearing white and grey matter on conventional MRI.

To explain the underlying mechanism of brain volume loss, in **chapter 5** we studied how the changes over a short time interval in both MRI and clinical measures of disease progression are related to the development of whole brain atrophy. To evaluate the rate of brain atrophy over time, two separate

time intervals were defined in which brain atrophy was measured. As such, the MRI and clinical metrics could be related with both concurrent and later interval atrophy rates, and additionally this set-up allowed studying the relation between the first interval atrophy rate and the second time interval atrophy rate. Cases were retrospectively selected from the available cohorts in the MAGNIMS centers. Two distinct patient groups were identified, one cohort of early RRMS with relatively active disease type and a second cohort with mixed disease type and relatively stable disease. The atrophy rates found in this study were in line with previous reports, being approximately 1% per year, although slightly higher in the early active disease cohort over the first interval. Only modest correlations were observed between atrophy rates and the changes in clinical and MRI measures for both intervals and cohorts. We concluded that the underlying pathology of atrophy is not completely reflected by current measures of clinical status, in vivo conventional MRI findings, or changes thereof over a short time interval. Additionally, we found only weak correlations between the atrophy rates in the first and second time intervals, suggesting that atrophy rates in MS vary over time in individual patients. As a result, the atrophy rates in the second interval could not be predicted well, even when the atrophy rate during the first interval was known.

In **chapter 6** we studied the functional motor system in RRMS patients during a simple motor task in relation to clinical parameters of disease progression. Previous studies have shown that regions that are activated by MS patients during the performance of simple motor tasks are different from those activated in healthy subjects. The regions recruited by the MS patients for simple motor tasks are part of pathways/networks that are recruited by healthy subjects only when more complex and difficult tasks have to be performed, but not for simple motor tasks. This might reflect an adaptive mechanism of an attempt of the brain of MS patients to cope with brain damage inflicted by the disease, helping to limit the clinical effects of the disease. So far, no direct relation has been shown between movement associated functional changes and clinical measures of disease progression, probably because of the limited number of patients in previous studies. Our study was embedded in the MAGNIMS collaboration to obtain high patient numbers and to explore the practical issues involved in multi-center fMRI application. Results confirmed previous studies with greater bilateral task-related activation in brain regions in patients. Additionally, patients showed higher activation in several brain regions correlated with lower hand dexterity. Both patients and healthy controls revealed higher activation with increasing age. These results imply that reorganization of the brain with recruitment of additional regions alters the clinical presentation of the disease, possibly limiting disability. Relatively limited variation was found between the participating centres, confirming the feasibility of a multicenter fMRI study.[15-17]

## General discussion

In this thesis, aspects of diagnosis and prognosis of patients with MS, were investigated using MRI.

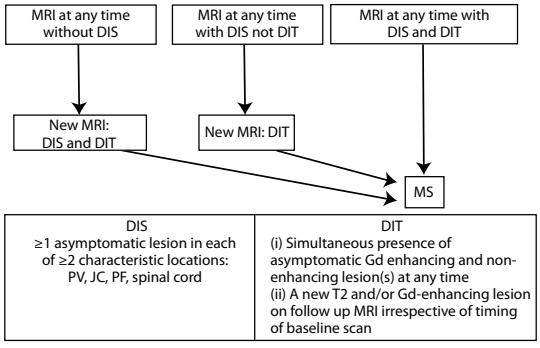
### 1. Diagnosis

This work confirmed the specificity of the MRI criteria incorporated in the diagnostic scheme for MS, both in a general diagnostic setting and in diagnostically difficult cases **(chapter 1 & 3)**. Furthermore, we have determined limitations of the criteria, reflected mainly in their sensitivity and complexity, especially regarding the use of spinal cord lesions **(chapter 2)**. Our observation, that the existing criteria are not straightforward and may be interpreted differently by different experts, was recently confirmed by Hawkes and Giovannoni.[18] To date, revisions have been applied [19] addressing the proper use of spinal cord lesions and criteria for DIT have been simplified.

*Technological advances improving the International Panel criteria*

As part of an ongoing collaborative effort within MAGNIMS, new criteria that have been simplified have been tested in typical CIS cohorts by Swanton and colleagues.[20] These criteria do appear to be robust and have been shown to provide somewhat higher sensitivity whilst maintaining specificity.[20-23] DIS criteria have been reduced to simply requiring a lesion in any two of the four typical MS locations; periventricular, juxtacortical, infratentorial and spinal cord. DIT can now be confirmed on a single

**Figure 1** New proposed diagnostic algorithm in patients with typical clinically isolated syndromes (CIS). From: Montalban, X. et al. Neurology 2010;74:427-434.




This algorithm only applies to patients with typical CIS, aged 14 to 50 years and after having performed a complete diagnostic workup. Gd = gadolinium-enhancing lesion; PV = periventricular; JC = juxtacortical; PF = posterior fossa; BS = brainstem; SC = spinal cord; DIS = dissemination in space; DIT = dissemination in time.

baseline scan if both enhancing and non-enhancing lesions are present or with a new T2 lesion on any follow-up scan.[20, 21, 24] Figure 1 shows the new proposed diagnostic algorithm. An additional advantage of recent criteria is that they do not need the use of gadolinium enhanced scans, saving both time and expenses. This clearly shows that the MRI criteria for MS are still being developed. Nevertheless, when conventional imaging at 1.5T is performed, further modifications to the diagnostic criteria are unlikely to yield much improvement in diagnostic certainty. This follows from the studies in this thesis, especially the work as described in chapter 4, which suggests that the additional diagnostic information that can be derived from the morphology and spatial distribution of lesions from conventional imaging is limited.

However, with the introduction of 3 Tesla and 7 Tesla MRI scanners, this may change. These higher fields enable higher resolution imaging with improved signal-to-noise–ratios, in theory improving lesion detection. It is to be expected that increased detection of small lesions in MS-specific brain regions (periventricular, infratentorial, etc.) might improve the diagnostic sensitivity of MRI, especially in early stages of the disease when small lesions that may have gone unnoticed at lower field strength could have important consequences for diagnosis and treatment. Initial results with 3 and 4 Tesla scanners in CIS patients did indeed reveal increased number of lesions compared to 1.5 Tesla images in anatomic regions which are important for the diagnosis of MS, namely in the juxtacortical, periventricular and the infratentorial region.[25] The current MRI criteria for diagnosing MS are based on MR images obtained at 1.0 and 1.5 Tesla. It would therefore be important for the IP to determine modified diagnostic criteria adapted to the new MR images acquired at 3 Tesla, or 7 Tesla when this should become widely available. The increase in lesion detection at these higher field strengths should be reflected by these modified criteria, probably leading to higher thresholds before patients can be diagnosed with MS. Therefore, further follow-up studies on the development of CDMS in cases of CIS are needed to determine these modified criteria. If this is performed successfully, these modified criteria will allow us to make the most of the improved lesion detection at higher field strengths, and hopefully thereby achieve better, and possibly also earlier, diagnosis.

*Pathological changes in the grey matter during MS progression*

Next to higher field strength, technological improvements have led to new MRI pulse sequences for image acquisition that enable better depiction of MS lesions. Especially the single slab 3D techniques hold great promise for replacing conventional 2D imaging in the future. Using this technique, high resolution isotropic 3D images of the brain can be acquired with various contrasts, including T1-weighted, T2-weighted and FLAIR images. In a comparative study, Moraal and colleagues found improved detection of MS lesions using this technique compared to conventional imaging.[26] Additionally, the use of 3D double inversion recovery (DIR) imaging in this study revealed the highest detection of grey matter lesions. Histopathological studies have shown that grey matter lesions are common and extensive in

MS but in vivo visualization of these lesions has been difficult with conventional imaging.[27] Gray matter pathology has been recognized as an important feature of MS pathology and could prove to be very relevant to disability progression and cognitive decline.[28] In a 3 year follow-up study in 80 patients with CIS, the presence of those lesions at baseline has been associated with a high risk for evolution to clinically definite MS and revealed higher specificity compared to the IP criteria for DIS.[29] This suggests that that incorporation of these lesions in diagnostic criteria could be beneficial.

Implementations of the DIR technique vary in terms of their signal-to-noise and contrast-to-noise ratios. Due to the two inversion pulses, much of the signal is suppressed, and depending on the exact implementation, this can lead to reduced detection of gray matter lesions. Before incorporating the gray matter MS lesions in diagnostic criteria, some consensus should be achieved on the pulse sequences to be used, for example whether to use 2D or 3D imaging, as well as on the rating of lesions on these images. The latter aspect is something that investigators have only recently been able to gain experience on, and recent work from MAGNIMS aims to devise criteria for detecting gray matter MS lesions on DIR images.[30]

*Inclusion of MS subgroups within the IP criteria*

Changes to diagnostic criteria may not only be called for by technological advances (higher field strengths, new pulse sequences) or improved understanding of pathological changes in MS (the importance of gray matter pathology); different clinical subgroups may also require different diagnostic criteria.

An important subgroup in current diagnostic criteria involves patients with PPMS. This subtype is characterized by slowly progressive disease without exacerbations and remissions that are used as clinical evidence for DIS and DIT in case of RRMS. Additionally, MRI in these patients show relatively low lesion burden but more severe involvement of the spinal cord.[31] Therefore, the current IP guidelines for diagnoses of PPMS includes the provision of at least 1 year continuous clinical progression of the disease with at least two of the following three features: a positive brain MRI (nine T2 lesions or four or more T2 lesions with positive visual evoked potentials), a positive spinal cord MRI (two focal T2 lesions) and positive CSF (oligoclonal IgG bands or increased IgG index).[19] As these separate criteria for PPMS add more complexity in the diagnosis of MS, recent research has focused on a unification of the RRMS and PPMS criteria. Within the MAGNIMS framework, Montalban and colleagues assessed the feasibility of similar criteria for diagnosis of DIS in all subtypes of MS and found levels of agreement between currently existing criteria for RRMS and PPMS that support the possibility to further revise the MS diagnostic algorithm to this aim.[32]

Other subgroups include pediatric patients and the non-western patient population. The IP diagnostic criteria, especially the MRI part, were derived from research in patients recruited from specialised centres and diagnosed by experienced neurologists, resulting in datasets with predominantly young

adults with clinically typical CIS. However, young children with MS, under the age of ten, differ the most from adult patients. They have a lower frequency of oligoclonal bands in their cerebrospinal fluid and are less likely to have discrete lesions on MRI. Similarly, Asian patients with MS tend to have fewer lesions in brain regions and larger lesions in the spinal cord with clinical characteristics associated with optical-spinal cord MS in the Caucasian population. Recently, modifications of the IP criteria were proposed for the pediatric patients. These revisions show higher sensitivity for DIS by requiring less total number of lesions, fewer periventricular lesions and presence of brainstem lesions instead of the more liberal criteria for infratentorial lesions as specified by the IP criteria. Additionally, the criterion for presence of juxtacortical lesions was discarded.[33] Likewise, recently proposed modifications to IP diagnostic criteria for Asians with MS allow more lenient criteria by limiting restrictions on spinal cord findings imposed by the IP and lowering the total number of lesions to four instead of nine as criterion for DIS.[34] These developments show similarity to the, previously mentioned, proposed Swanton criteria for CIS patients in their need for fewer lesions in limited MS-specific brain regions compared to the IP criteria. Perhaps the upcoming advances in MRI, as outlined previously, will further diminish the current differences between MS subgroups by revealing more specific or sensitive MRI markers for MS and maybe enable uniform criteria for diagnosis.

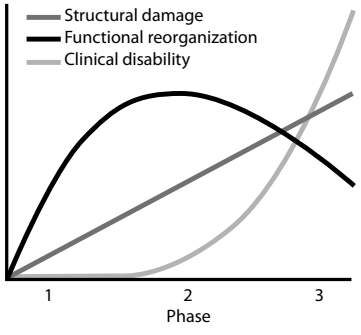
## 2. Prognosis: determinants of progression

Challenges to confront in the future include provision of parameters better predicting the disease course in individual patients to identify individuals who most need therapeutic intervention and those who least need it. However, the mechanisms leading to deficit in the disease course of MS are yet not fully understood. In addition to focal inflammatory white matter lesions, pathological changes occur in the normal appearing white and gray matter and neuroaxonal loss, as reflected by brain atrophy, develops early in the disease. Whether these processes are interrelated has to be further disentangled, but pathology data suggest that inflammation and neurodegeneration occur in parallel.[35, 36] Clarification of these processes might further explain the cause of development of disability and aid in providing robust prognostic (MRI) parameters. Ultimately, these (probably clinical and paraclinical) findings need to be translated from group to individual level to provide efficient and standardized tools to evaluate MS therapies in general hospital practice.

In the study presented in **chapter 5** of this thesis we aimed to predict the rate of neurodegeneration, using the rate of change of whole brain volume as a surrogate marker. However, only limited correlations could be found on individual patient level. Additionally, the development of disability was difficult to predict from changes in focal lesion loads, clinical assessments of disease progression and atrophy measurements. The time course of atrophy and differences between the subgroups of MS were further studied within the MAGNIMS network.[37] A large MS patient group, not treated for the

disease, was assembled from the different participating centres and atrophy over two time points measured. In this study the heterogeneity in atrophy rates largely disappeared between subgroups when corrected for baseline atrophy state, as reflected by the normalised brain volume. This suggests a rather even proceeding of atrophy over the course of MS with a rate independent of the MS subtype. Although recent work from Minneboo and colleagues[38] revealed added information of brain atrophy for predicting progression of disability in early MS and work from Lukas and colleagues revealed better prediction when rate of ventricle enlargement is used as predictor instead (C. Lukas et al., JNNP, in press) the predictive property of conventional MRI for the development of disability has only shown mild correlations in previous studies. This is known as the clinicoradiologic dissociation.[39] This might, at least partially, be explained by an adaptive capacity of the brain, limiting the clinical consequences of inflicted brain damage as appreciated with conventional MRI. Figure 2 represents a graphical interpretation of this process. By recruiting additional brain regions, normally active in complex or specific tasks, basic brain functions or tasks can be maintained on a certain level. This process is known as functional reorganization. As a result, the direct relationship between MRI derived metrics of brain damage and clinical measurements of disease progression get obscured. With the use of fMRI, the activated brain regions during a specific task can be visualized and the study in **chapter 6**, amongst other studies, revealed the activation of such additional brain regions in MS patients compared to healthy controls whilst performing a simple motor task. Additional fMRI studies within the MAGNIMS network collaboration revealed supportive evidence that enhancement of effective connectivity in

**Figure 2** Initially, very little structural damage causes a strong response in functional reorganization and hyperactivation in the brain, resulting in low disability and cognitive preservation in phase 1. After functional reorganization reaches its peak in phase 2 and decreases thereafter, cognitive impairment and disability progressively develop throughout phase 3.
From: Schoonheim, M. M. et al. Neurology 2010;74:1246-1247



brain networks may provide an (other) important compensatory mechanism in MS.[16] Furthermore, it was demonstrated that attenuation of the fMRI response during repeated task execution, considered to be a physiological process, is preserved in MS.[17] In future research these fMRI findings can be combined with conventional MRI metrics of brain damage to further explore the reactive changes of the brain. Ultimately, as outlined by Schoonheim and colleagues, combinations of task based fMRI, resting state fMRI and so-called graph analysis describing brain network efficiency, specific therapeutic targets in the brain might be revealed for cognitive rehabilitation or pharmacotherapy.[40]
Besides focal lesions on conventional imaging, changes in diffusely abnormal (dirty) white matter (DAWM) and normal appearing white matter (NAWM) have gained attention in their relationship with development of disability in MS. A recent study by Seewann and colleagues showed changes most likely associated with chronic ongoing inflammation and axonal pathology in DAWM regions.[41] Further research is needed to analyze the role of these findings in disease burden rating for MS but might further diminish the radiological-clinical dissociation.

In conclusion, we confirmed the diagnostic properties of MRI in the earliest stages of MS, in patients with a CIS. However, within the limits of conventional T1 and T2 weighted imaging, we were not able to significantly improve the MRI part of the current IP diagnostic scheme for MS. Though, within MAGNIMS collaboration, simplified and more sensitive criteria have been proposed that maintained current specificity. We discussed technological improvements and new insights in the development of MS that, in future research, might lead to higher diagnostic accuracy.
In the second part of this thesis we applied nonconventional imaging techniques in patients with MS, including atrophy measurements and fMRI, in order to further explain the mechanisms leading to development of disability in several MS subgroups. However, current correlations between these measures and (future) disability remained weak. We argued that adaptive capabilities of the brain in reaction to inflicted damage by MS might to some degree be responsible for this phenomenon and research presented in this thesis supports this assumption. Future research with fMRI and expected improvement of methods to analyze brain networks hold great promise for the future to further explain these processes in the brain.

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